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EXAMINER	
FORMAN, BETTY J	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

S.M.

Office Action Summary	Application No.	Applicant(s)	
	09/394,230	GUNDERSON ET AL.	
	Examin r	Art Unit	
	BJ Forman	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 27 October 2003 has been entered.

Status of the Claims

2. This action is in response to papers filed 27 October 2003 in which claims 1 and 12 were amended. All of the amendments have been thoroughly reviewed and entered.

The previous rejections in the Office Action dated 26 June 2003 are maintained. All of the arguments have been thoroughly reviewed and are discussed below.

New grounds for rejection are discussed.

Claims 1-18 are under prosecution.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. Claims 1-4, 6-10, 12-15 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Lockhart et al (WO/97,27317, published 31 July 1997).

Regarding Claim 1, Lockhart et al disclose a method of determining the presence of a mutation in a target polynucleotide, comprising the steps of providing at least two identical polynucleotide probe arrays, each array comprising probes, wherein each probe comprises a double stranded region and a single-stranded n-mer overhang region such that the overhangs in each array constitute a complete set of n-mers (Fig. 13; page 71, lines 9-29 and page 74, lines 1-12) hybridizing the target polynucleotide to said overhangs of probe polynucleotides in one array to generate a target hybridization pattern hybridizing a reference polynucleotide to said overhangs of probe polynucleotides in a second array to generate a reference hybridization pattern and determining the presence of a mutation in the target polynucleotide by normalizing intensity differences of hybridized probes in the reference and target hybridization patterns comparing intensity differences of probes in the reference and target hybridization patterns and determining whether a mutation is present in the target polynucleotide (Example 20, pages 155-158).

Regarding Claim 2, Lockhart et al disclose the method of claim 1, wherein in step b), the hybridized target polynucleotide is ligated to the probe (Fig. 13a and page 71, lines 9-29).

Regarding Claim 3, Lockhart et al disclose the method of claim 1, wherein in step c), the hybridized reference polynucleotide is ligated to the probe (Fig. 13a; page 71, lines 9-29 and Example 20, pages 155-158).

Regarding Claim 4, Lockhart et al disclose the method of claim 1, wherein the overhangs have free 5' ends (Fig. 13a).

Regarding Claim 6, Lockhart et al disclose the method of claim 1, wherein the n-mer comprises from about 4 to about 50 nucleotides (page 74, lines 1-12).

Regarding Claim 7, Lockhart et al disclose the method of claim 1, wherein the mutation is a substitution mutation (Fig. 31-32 and page 157, line 10-page 158, line 9).

Regarding Claim 8, Lockhart et al disclose the method wherein the mutation is a deletion mutation i.e. identity (Fig. 31-32 and page 14, lines 6-17).

Regarding Claim 9, Lockhart et al disclose the method of claim 1, wherein the mutation is an insertion mutation i.e. identity (page 14, lines 6-17).

Regarding Claim 10, Lockhart et al disclose the method of claim 1, in which said target polynucleotide is selected from the group consisting of: a cystic fibrosis transmembrane conductance regulator gene, a p53 gene, a mitochondrial DNA, or an HIV gene (Fig. 32 and page 21, line 22-page 22, line 2).

Regarding Claim 12, Lockhart et al disclose a method of determining whether two or more target polynucleotides are identical, comprising the steps of providing at least two identical polynucleotide probe arrays, each array comprising probes, wherein each probe comprises a double-stranded region and a single-stranded n-mer overhang region such that the overhangs in each array constitute a complete set of n-mers (Fig. 13; page 71, lines 9-29 and page 74, lines 1-12) hybridizing first target polynucleotide to said overhangs of probe polynucleotides in one array to generate a first hybridization pattern hybridizing second target

polynucleotide to said overhangs of probe polynucleotides in a second array to generate a second hybridization pattern and normalizing intensity differences of hybridized probes in the first and second hybridization patterns, comparing intensity differences of probes in the first and second hybridization patterns and determining whether two or more target polynucleotides are identical (Example 20, pages 155-158).

Regarding Claim 13, Lockhart et al disclose the method of claim 12, wherein in step b), the hybridized target polynucleotide is ligated to the probe (Fig. 13a and page 71, lines 9-21).

Regarding Claim 14, Lockhart et al disclose the method of claim 12, wherein in step c), the hybridized reference polynucleotide is ligated to the probe (Fig. 13a; page 71, lines 9-21 and Example 20, pages 155-158).

Regarding Claim 15, Lockhart et al disclose the method of claim 12, wherein the overhangs have free 5' ends (Fig. 13a).

Regarding Claim 17, Lockhart et al disclose the method of claim 12, wherein the n-mer comprises from about 4 to about 50 nucleotides (page 74, lines 1-12).

5. Claims 1-4, 6-10, 12-15 and 17 are rejected under 35 U.S.C. 102(e) as being anticipated by Lockhart et al (U.S. Patent No. 6,344,316, filed 25 June 1997).

The applied reference has a common inventor and assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived

from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Regarding Claim 1, Lockhart et al disclose a method of determining the presence of a mutation in a target polynucleotide, comprising the steps of providing at least two identical polynucleotide probe arrays, each array comprising probes, wherein each probe comprises a double stranded region and a single-stranded n-mer overhang region such that the overhangs in each array constitute a complete set of n-mers (Fig. 13; Column 48, lines 26-47; and Column 50, lines 14-31) hybridizing the target polynucleotide to said overhangs of probe polynucleotides in one array to generate a target hybridization pattern hybridizing a reference polynucleotide to said overhangs of probe polynucleotides in a second array to generate a reference hybridization pattern and determining the presence of a mutation in the target polynucleotide by normalizing intensity differences of hybridized probes in the reference and target hybridization patterns comparing intensity differences of probes in the reference and target hybridization patterns and determining whether a mutation is present in the target polynucleotide (Column 107, lines 4-49).

Regarding Claim 2, Lockhart et al disclose the method of claim 1, wherein in step b), the hybridized target polynucleotide is ligated to the probe (Fig. 13a and Column 48, lines 26-47).

Regarding Claim 3, Lockhart et al disclose the method of claim 1, wherein in step c), the hybridized reference polynucleotide is ligated to the probe (Fig. 13a; Column 48, lines 26-47; and Column 107, lines 4-49).

Regarding Claim 4, Lockhart et al disclose the method of claim 1, wherein the overhangs have free 5' ends (Fig. 13a).

Regarding Claim 6, Lockhart et al disclose the method of claim 1, wherein the n-mer comprises from about 4 to about 50 nucleotides (Column 50, lines 14-19).

Regarding Claim 7, Lockhart et al disclose the method of claim 1, wherein the mutation is a substitution mutation (Fig. 31-32 and Column 107, lines 50-67).

Regarding Claim 8, Lockhart et al disclose the method wherein the mutation is a deletion mutation i.e. identity (Column 9, lines 49-64).

Regarding Claim 9, Lockhart et al disclose the method of claim 1, wherein the mutation is an insertion mutation i.e. identity (Column 9, lines 49-64).

Regarding Claim 10, Lockhart et al disclose the method of claim 1, in which said target polynucleotide is selected from the group consisting of: a cystic fibrosis transmembrane conductance regulator gene, a p53 gene, a mitochondrial DNA, or an HIV gene (Fig. 32 and Column 14, lines 46-61).

Regarding Claim 12, Lockhart et al disclose a method of determining whether two or more target polynucleotides are identical, comprising the steps of providing at least two identical polynucleotide probe arrays, each array comprising probes, wherein each probe comprises a double stranded region and a single-stranded n-mer overhang region such that the overhangs in each array constitute a complete set of n-mers ((Fig. 13; Column 48, lines 26-47; and Column 50, lines 14-31) hybridizing first target polynucleotide to said overhangs of probe polynucleotides in one array to generate a first hybridization pattern hybridizing second target polynucleotide to said overhangs of probe polynucleotides in a second array to generate a second hybridization pattern and normalizing intensity differences of hybridized probes in the first and second hybridization patterns, comparing intensity differences of probes in the first and second hybridization patterns and determining whether two or more target polynucleotides are identical (Column 107, lines 4-67).

~~Regarding Claim 13, Lockhart et al disclose the method of claim 12, wherein in step b),~~ the hybridized target polynucleotide is ligated to the probe (Fig. 13a and Column 48, lines 26-47).

Regarding Claim 14, Lockhart et al disclose the method of claim 12, wherein in step c), the hybridized reference polynucleotide is ligated to the probe (Fig. 13a; Column 48, lines 26-47; and Column 107, lines 4-49).

Regarding Claim 15, Lockhart et al disclose the method of claim 12, wherein the overhangs have free 5' ends (Fig. 13a).

Regarding Claim 17, Lockhart et al disclose the method of claim 12, wherein the n-mer comprises from about 4 to about 50 nucleotides (Column 50, lines 14-19).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 5 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lockhart et al (WO/97,27317, published 31 July 1997) in view of Cantor (U.S. Patent No. 5,631,134, filed 5 June 1995).

Regarding Claims 5 and 16, Lockhart et al disclose a method of determining the presence of a mutation in a target polynucleotide, comprising the steps of providing at least two identical polynucleotide probe arrays, each array comprising probes, wherein each probe comprises a double stranded region and a single-stranded n-mer overhang region such that the overhangs in each array constitute a complete set of n-mers (Fig. 13; page 71, lines 9-29 and

page 74, lines 1-12) hybridizing the target polynucleotide to said overhangs of probe polynucleotides in one array to generate a target hybridization pattern hybridizing a reference polynucleotide to said overhangs of probe polynucleotides in a second array to generate a reference hybridization pattern and determining the presence of a mutation in the target polynucleotide by normalizing intensity differences of hybridized probes in the reference and target hybridization patterns comparing intensity differences of probes in the reference and target hybridization patterns and determining whether a mutation is present in the target polynucleotide (Example 20, pages 155-158) wherein the overhangs have free 5' ends (Fig. 13a). Lockhart et al do not teach the overhangs have free 3' ends.

However, overhangs having free 3' ends were well known in the art at the time the claimed invention was made as taught by Cantor et al who teach that the arrayed probes having free 3' overhangs provides enhanced sequence stringency in detecting 5' terminal nucleotides of the target sequence (Column 12, lines 9-19). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the free 3' overhang of Cantor to the overhang probes of Lockhart et al for the expected benefits of enhanced sequence stringency in detecting 5' terminal nucleotides of the target sequence as taught by Cantor (Column 12, lines 9-19).

8. Claims 11 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lockhart et al (WO/97,27317, published 31 July 1997) in view of Southern (U.S. Patent No. 5,700,637, filed 19 April 1994).

Regarding Claims 11 and 18, Lockhart et al disclose a method of determining the presence of a mutation in a target polynucleotide, comprising the steps of providing at least two identical polynucleotide probe arrays, each array comprising probes, wherein each probe

comprises a double stranded region and a single-stranded n-mer overhang region such that the overhangs in each array constitute a complete set of n-mers (Fig. 13; page 71, lines 9-29 and page 74, lines 1-12) hybridizing the target polynucleotide to said overhangs of probe polynucleotides in one array to generate a target hybridization pattern hybridizing a reference polynucleotide to said overhangs of probe polynucleotides in a second array to generate a reference hybridization pattern and determining the presence of a mutation in the target polynucleotide by normalizing intensity differences of hybridized probes in the reference and target hybridization patterns comparing intensity differences of probes in the reference and target hybridization patterns and determining whether a mutation is present in the target polynucleotide (Example 20, pages 155-158) wherein the target-hybridized array and the reference-hybridized array are compared (page 156, line 29-page 157, line 7) which clearly suggests that the arrays are proximal to each other. But they do not specifically teach that the arrays are arranged in parallel.

However, Southern teaches the similar method wherein the arrays are arranged in parallel i.e. stripes (Column 7, lines 12-22) whereby numerous sequence variations are analyzed simultaneously wherein each stripe corresponds to a different sequence variation. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the parallel arrays (i.e. strips) of Southern for the array comparison of Lockhart et al for the expected benefit of analyzing numerous mutations simultaneously as taught by Southern (Column 7, lines 23-26).

9. Claims 1-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cantor et al. (U.S. Patent No. 5,631,134, filed 5 June 1995) in view of Southern (U.S. Patent No. 5,700,637, filed 19 April 1994) and Lipshutz et al (U.S. Patent No. 6,300,063, filed 29 November 1995).

Regarding Claim 1, Cantor et al. teach a method of determining the presence of a mutation in a target polynucleotide comprising the steps of providing a polynucleotide probe array wherein each probe comprises a double strand region and a single stranded n-mer overhang region; hybridizing a target polynucleotide to said overhangs in the array to generate a target hybridization pattern; and determining the presence of a mutation in the target polynucleotide by analyzing hybridization patterns (Column 8, lines 1-12) wherein the probes are designed to identify mutations (Column 4, lines 5-8) wherein the a single stranded n-mer overhang region is "preferably" about 4 to 20 nucleotides in length (Column 5, lines 60-65) and wherein the set of probes on the array comprises every possible n-mer (Column 6, lines 3-5). Cantor et al. do not teach hybridizing a reference polynucleotide to a second array and determining the presence of a mutation by comparing the reference and target hybridization patterns. However, the comparison of reference and target hybridization patterns to determine the presence of a mutation was known and routinely practiced in the art at the time the claimed invention was made. Specifically, Southern teaches a similar method for determining the presence of a mutation in a target polynucleotide comprising hybridizing a target polynucleotide to array and a reference polynucleotide to a second array (Column 7,lines 10-31) and determining the presence of a mutation by comparing reference and target hybridization patterns without sequencing the target polynucleotide (Column 3, lines 58-62) wherein the n-mer arrays are complete n-mer arrays (Column 6, lines 8-27). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the complete n-mer hybridization detection and analysis of Cantor et al. with the

complete n-mer hybridization comparison analysis of Southern whereby comparing hybridization patterns reveals differences between the target and reference and eliminates the need for sequencing the target sequence (Column 3, lines 52-62) and wherein the hybridizations are extremely sensitive because complete n-mer hybridizations are performed under highly stringent conditions to discriminate between single mismatch sequences as taught by Southern (Column 10, line 57-67-Column 11, line 4) for the expected benefits of identifying mutations accurately, efficiently and economically i.e. identifying mutations under highly stringent conditions without the time and labor consuming sequencing reactions.

Cantor et al and Southern do not teach the arrays comprise perfect match and mismatch probes wherein mutation determination is via normalizing hybridization intensities utilizing the mismatch and perfect match probes. However, Lipshutz et al teach a similar method comprising hybridizing target polynucleotides to probes having an overhang (Column 5,lines 21-24) on an array comprising perfect match and mismatch probes (Example 2, Column 12, lines 15-32) wherein normalization intensity differences comprises dividing the perfect match hybridization intensity by the hybridization intensity for mismatch probes (Column 9, line 36-Column 10, line 56). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the normalization of Lipshutz et al to the mutation detection of Cantor et al and Southern to thereby easily and accurately identify mutations as taught by Lipshutz et al (Column 9, line 36-Column 10, line 56).

Regarding Claim 2, Cantor et al. teach the hybridized polynucleotide is ligated to the probe (Column 8, lines 8-9).

Regarding Claim 3, Cantor et al. teach the hybridized polynucleotide is ligated to the probe (Column 8, lines 8-9). Cantor et al. do not discuss the reference polynucleotide. However, reference polynucleotides were known to one of ordinary skill in the art as discussed above and the skilled practitioner would have known that for comparison purposes, a target and reference polynucleotide would be treated equally i.e. ligated to the probe.

Regarding Claim 4, Cantor et al. teach the overhangs have free 5' ends (Column 12, lines 46-49 and Fig. 1B).

Regarding Claim 5, Cantor et al. teach the overhangs have free 3' ends (Column 12, lines 38-45 and Fig. 1A).

Regarding Claim 6, Cantor et al. teach the n-mer comprises from about 4 to 50 nucleotides (Column 12, lines 57-60).

Regarding Claims 7-9, Cantor et al. teach the mutation is a single nucleotide mutation (Column 10, lines 38-40). Cantor et al. do not teach the single nucleotide mutation is a substitution (Claim 7), a deletion (Claim 8) and an insertion (Claim 9). However, one skilled in the art at the time the claimed invention was made would have known that the single nucleotide mutations taught by Cantor et al. include the claimed substitution, deletion and insertion mutations.

Regarding Claim 10, Cantor et al teach the method wherein single nucleotide mutations are identified wherein the identification quickly, efficiently and easily detects inherited mutations which cause disease and DNA depended phenotype and somatic variations (Column 10, lines 38-45). Cantor et al. do not teach the target polynucleotide is selected from the recited sequences. However, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Cantor et al. with the teachings of Cantor et al. to obtain the claimed invention because the skilled practitioner in the art would have been motivated with a reasonable expectation of success to apply the mutation detection teaching of Cantor et al. to sequences known to contain single nucleotide mutations for the obvious benefit of detecting clinically relevant mutations quickly, efficiently and easily as taught by Cantor et al.

Regarding Claim 11, Cantor et al. do not teach parallel arrays. However, Southern teaches the similar method wherein the arrays are arranged in parallel i.e. stripes (Column 7, lines 12-22) whereby numerous sequence variations are analyzed simultaneously wherein each

stripe corresponds to a different sequence variation. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the single array of Cantor et al. with the parallel arrays (i.e. strips) of Southern for the expected benefit of analyzing numerous mutations simultaneously as taught by Southern (Column 7, lines 23-26).

Regarding Claim 12, Cantor et al. teach a method of determining relatedness two or more polynucleotides comprising the steps of providing a polynucleotide probe array wherein each probe comprises a double stranded region and a single stranded n-mer overhang region such that the over hangs in each array constitute a complete set of n-mers; hybridizing a target polynucleotide to said overhangs in the array to generate a hybridization pattern and analyzing the hybridization patterns (Column 8, lines 1-10) wherein the a single stranded n-mer overhang region is "preferably" about 4 to 20 nucleotides in length (Column 5, lines 60-65) and wherein the set of probes on the array comprises every possible n-mer (Column 6, lines 3-5). Cantor et al. do not teach the method comprising two identical arrays wherein the target polynucleotide is hybridized to one array and a second target polynucleotide is hybridized to a second array. However, the comparison of hybridization patterns to determine if two or more sequences are identical was known and routinely practiced in the art at the time the claimed invention was made. Specifically, Southern teaches a similar method for determining whether two or more target polynucleotides are identical comprising providing at least two identical polynucleotide probe arrays; hybridizing a first polynucleotide to one array stripe and a second polynucleotide to a second array stripe (Column 7, lines 10-31) and comparing the first and second hybridization patterns without sequencing the target polynucleotide (Column 3, lines 58-62). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the complete n-mer hybridization detection and analysis of Cantor et al. with the complete n-mer hybridization comparison analysis of Southern whereby comparing hybridization patterns reveals differences between sequences and eliminates the need for sequencing the sequences (Column 3, lines 52-62) and wherein the hybridizations are

extremely sensitive because complete n-mer hybridizations are performed under highly stringent conditions which discriminate between single mismatch sequences (Column 10, line 57-67-Column 11, line 4) for the expected benefits of determining sequence similarity accurately, efficiently and economically i.e. determining sequence similarity under highly stringent conditions without the time and labor consuming sequencing reactions.

Cantor et al and Southern do not teach the arrays comprise perfect match and mismatch probes wherein mutation determination is via normalizing hybridization intensities utilizing the mismatch and perfect match probes. However, Lipshutz et al also teach a similar method comprising hybridizing target polynucleotides to probes having an overhang (Column 5,lines 21-24) on an array comprising perfect match and mismatch probes (Example 2, Column 12, lines 15-32) wherein normalization intensity differences comprises dividing the perfect match hybridization intensity by the hybridization intensity for mismatch probes (Column 9, line 36-Column 10, line 56). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the normalization of Lipshutz et al to the mutation detection of Cantor et al and Southern to thereby easily and accurately identify mutations as taught by Lipshutz et al (Column 9, line 36-Column 10, line 56).

Regarding Claim 13, Cantor et al. teach the hybridized polynucleotide is ligated to the probe (Column 8, lines 8-9).

Regarding Claim 14, Cantor et al. teach the hybridized polynucleotide is ligated to the probe (Column 8, lines 8-9). Cantor et al. do not discuss the reference polynucleotide. However, reference polynucleotides were known to one of ordinary skill in the art as discussed above and the skilled practitioner would have known that for comparison purposes, a target and reference polynucleotide would be treated equally i.e. ligated to the probe.

Regarding Claim 15, Cantor et al. teach the overhangs have free 5' ends (Column 12, lines 46-49 and Fig. 1B).

Regarding Claim 16, Cantor et al. teach the overhangs have free 3' ends (Column 12, lines 38-45 and Fig. 1A).

Regarding Claim 17, Cantor et al. teach the n-mer comprises from about 4 to 50 nucleotides (Column 12, lines 57-60).

Regarding Claim 18, Cantor et al. do not teach parallel arrays. However, Southern teaches the similar method wherein the arrays are arranged in parallel i.e. stripes (Column 7, lines 12-22) whereby numerous sequence variations are analyzed simultaneously wherein each stripe corresponds to a different sequence variation. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the single array of Cantor et al. with the parallel arrays (i.e. strips) of Southern for the expected benefit of analyzing numerous mutations simultaneously as taught by Southern (Column 7, lines 23-26).

Response to Arguments

10. Applicant argues that the references fail to disclose all of the claimed element e.g. Cantor et al do not teach hybridizing reference polynucleotides to a second array; Southern et al do not teach reference polynucleotides or probes having a double stranded region and n-mer overhangs; and Lipshutz et al do not teach separately hybridizing target and reference polynucleotides. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant argues that the combination of references and especially Cantor fails to "effectively" teach use of a complete set of n-mers. Applicant further argues that Cantor teaches away from the use of complete n-mers by stating that it would be hard to make an array with such large numbers, by stating that the set of probes need not contain a complete set and by failing to teach how to make and use a complete set on n-mers. The argument has been considered but is not found persuasive because a careful reading of Cantor clearly

teaches a complete set of n-mers wherein the complete set 4-mers comprises 256 different probes (e.g. Column 6, lines 3-9) and a complete set of 5-mers comprises 1024 probes (Column 12, lines 57-60). Furthermore, it is only with respect to 20-mers that Cantor suggest such a complete set becomes "a very large number" (Column 6, lines 12-13). Contrary to Applicant's assertion, nowhere in the cited passage does Cantor describe "how hard it would be to make an array with such a large number of probes".

Applicant argues that the teaching of Cantor would not provide one of ordinary skill in the art a reasonable expectation of success and that one of ordinary skill would not reasonably expect from the confusing and speculative teaching of Cantor et al to produce an array with a complete set of n-mer that could successfully work in the methods of the present invention. Applicant cites passages of Cantor et al which differ in from the instant invention to support the conclusion that the array of Cantor et al would not work successfully. Applicant further argues that the combination of Southern and Lipshutz with that of Cantor does not provide a reasonable expectation of success.

The arguments have been considered but are not found persuasive for numerous reasons. First, Cantor et al specifically teach a complete n-mer (Column 6, lines 3-5) and they teach clearly teach probe arrays (Column 7, lines 12-24 and Claim 1-18). Second, the courts have stated that the arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965).

> Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant. (see MPEP § 716.01(c))

Finally, the courts have further stated that when the reference relied on expressly anticipates or makes obvious all of the elements of the claimed invention, the reference is presumed to be operable. Once such a reference is found, the burden is on applicant to provide

facts rebutting the presumption of operability. In re Sasse, 629 F.2d 675, 207 USPQ 107 (CCPA 1980) (See MPEP § 2121 and § 716.07).

For the reasons stated above, Applicant's arguments regarding no reasonable expectation of success are not found persuasive.

Applicant argues that the examiner has used hindsight reconstruction to arrive at the instant invention. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Applicant further argues that there is no motivation to combine the teachings of Cantor with those of Southern and Lipshutz. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the motivation to combine was clearly provided in the final office action as summarized below.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the complete n-mer hybridization detection and analysis of Cantor et al. with the complete n-mer hybridization comparison analysis of Southern whereby comparing hybridization patterns reveals differences between the target and reference and eliminates the need for sequencing the target sequence (Column 3, lines 52-62) and wherein the hybridizations are extremely sensitive because complete n-mer hybridizations are performed under highly stringent conditions to discriminate between single mismatch

sequences as taught by Southern (Column 10, line 57-67-Column 11, line 4) for the expected benefits of identifying mutations accurately, efficiently and economically i.e. identifying mutations under highly stringent conditions without the time and labor consuming sequencing reactions.

Cantor et al and Southern do not teach the arrays comprise perfect match and mismatch probes wherein mutation determination is via normalizing hybridization intensities utilizing the mismatch and perfect match probes. Lipshutz et al also teach a similar method comprising hybridizing target polynucleotides to probes having an overhang (Column 5,lines 21-24) on an array comprising perfect match and mismatch probes (Example 2, Column 12, lines 15-32) wherein normalization intensity differences comprises dividing the perfect match hybridization intensity by the hybridization intensity for mismatch probes (Column 9, line 36-Column 10, line 56). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the normalization of Lipshutz et al to the mutation detection of Cantor et al and Southern to thereby easily and accurately identify mutations as taught by Lipshutz et al (Column 9, line 36-Column 10, line 56).

Conclusion

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (703) 306-5878 until 13 January 2004. Starting 14 January 2004, the examiner's phone number will be (517) 272-0741. The examiner can normally be reached on 6:00 TO 3:30 Monday through Thursday and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (703) 308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 308-8724 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196. Starting 14 January 2003, the receptionist telephone number will be (517)-272-0507.

BJ Forman, Ph.D.
Primary Examiner
Art Unit: 1634
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